FILED
2012 May-18 PM 04:25
U.S. DISTRICT COURT
N.D. OF ALABAMA

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

IN RE: CHANTIX (VARENICLINE) PRODUCTS LIABILITY LITIGATION	Master File No. 2:09-CV-2039-IPJ MDL No. 2092
This Document Relates To: ALL CASES	

DEFENDANT PFIZER INC'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION TO EXCLUDE OPINIONS OFFERED BY PLAINTIFFS' EXPERT DR. RICHARD E. OLMSTEAD

(MEMORANDUM 1 OF 6)

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PRELIMINARY STATEMENT

Plaintiffs' expert Dr. Richard E. Olmstead's general causation opinion is based on a single table of clinical trial data (and subsequent iterations of that table) that Pfizer submitted to FDA in 2005. The table includes only a subset of the total Chantix clinical trials. It also includes a mixture of different studies, some of which do not include a control group. Dr. Olmstead performs numerous statistical analyses of the data in this table, which he claims show a statistically significant association between Chantix use and depression-related events. Dr. Olmstead admits that the table is outdated; it includes trials that lack a control group; and it does not reflect the current state of the clinical trial evidence today.

For three reasons, Dr. Olmstead has no reliable basis to conclude that his analyses demonstrate a valid statistical association between Chantix and depression. First, by combining controlled and uncontrolled clinical trial data, Dr. Olmstead's analyses do not reliably account for the background risk of suicide and depression among smokers in general. In *McClain v. Metabolife International, Inc.*, the Eleventh Circuit explained that "[a] reliable methodology should take into account the background risk." 401 F.3d 1233, 1243 (11th Cir. 2005). Because Dr. Olmstead fails to account for the background risk of suicide and depression among smokers, his findings are unreliable.

Second, Dr. Olmstead's statistical analyses are based on unreliable methods. He uses a statistical test that is not generally accepted within the scientific community and he does not adjust for the inflated error rate caused by his multiple analyses.

Third, Dr. Olmstead fails to account for the confounding effect of nicotine withdrawal. He admits that quitting smoking is associated with withdrawal symptoms such as depression, yet he fails to "account for the roles of bias [and] confounding factors" in his analyses. *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 604 (D. N.J. 2002).

Even if he could establish a valid statistical association, Dr. Olmstead has no reliable basis to conclude that any difference he observed in his analyses reflects an actual causal relationship. Dr. Olmstead fails to consider the totality of the available scientific evidence; instead, he cherry-picks a single table from a 5,000+ page document to support his opinions. He also ignores more recent analyses of the clinical trial data and observational studies, which were performed by FDA and other independent scientists, and which found no link between Chantix and depression. Finally, Dr. Olmstead ignores the lack of a dose response between Chantix and depression-related events. According to the Eleventh Circuit, the dose-response relationship is "the single most important factor to consider" and "the hallmark of the science of toxic torts." *McClain*, 401 F.3d at 1240, 1242. Dr.

Olmstead's willingness to ignore the totality of the available evidence and the lack of a dose-response relationship for Chantix further demonstrates the unreliability of his opinions.

STATEMENT OF FACTS

I. QUALIFICATIONS, RELEVANT EXPERIENCE, AND KNOWLEDGE

Dr. Richard E. Olmstead is a researcher affiliated with the University of California, Los Angeles ("UCLA"). *See* Richard Olmstead Curriculum Vitae ("Olmstead CV") at 1 (Ex. 28). He is not a professor at the school. *See* Deposition of Dr. Richard Olmstead, Mar. 21, 2012, at 381, 399 ("Olmstead Dep.") (Ex. 45). He earned his Ph.D. in psychology, but he does not have a medical degree or license to practice psychology. *See* Olmstead CV at 1; Olmstead Dep. at 416, 419.

Dr. Olmstead never has published a paper in a statistical journal or served as an editor or peer-reviewer for a statistics journal. *See* Olmstead Dep. at 401-02. He never has performed a statistical analysis for an FDA-approved medication. *See id.* at 401-02, 405, 415. Dr. Olmstead has published research on the neuropsychiatric effects of nicotine and smoking cessation therapies, but he offers no opinions in those areas. *See id.* at 79-80.

Dr. Olmstead also has virtually no experience with meta-analyses. He recognizes there are published rules for performing meta-analyses, but he cannot identify any publications describing those rules. *See id.* at 122-23. He never has

published a meta-analysis that he conducted himself; as he admitted, "I haven't done a lot of meta-analysis work in my time." *Id.* at 154; *see id.* at 122-23, 397.

II. DR. RICHARD OLMSTEAD'S UNRELIABLE CAUSATION OPINIONS

A. Dr. Olmstead Lacks a Sufficient Foundation for Relying on the Data that Form the Bases of His Analyses.

In 2005, in connection with its New Drug Application ("NDA") for Chantix, Pfizer submitted to FDA a Summary of Clinical Safety, which consisted of a 153-page narrative document describing data from the Chantix clinical trials, as well as nearly 5,000 pages of tables with data from those clinical trials. *See generally* Summary of Clinical Safety, Oct. 18, 2005 (Ex. 51). Dr. Olmstead reviewed one of the tables, the back-up data for that table, and subsequent iterations of the table, which contain additional data from 2007 and 2009. *See* Expert Report of Dr. Richard Olmstead, Dec. 7, 2011, at 5 ("Olmstead Rep.") (Ex. 13). He then performed statistical analyses of those data and presented his results. *See id.* at 8-9, 11, 13. He concluded that: (1) Chantix doubles the risk of depression-related events; (2) the increased risk did not change appreciably as Pfizer collected additional data; and (3) reasonable evidence of a causal association existed by at least 2005. *See id.* at 7, 10, 13-14, 16.

Dr. Olmstead bases his 2005 analyses on two portions of the available data: (1) Table 38 in the Summary of Clinical Safety, which summarized certain

psychiatric disorders seen in four placebo-controlled trials; and (2) a larger "data compilation" listing all adverse events that occurred in eight trials conducted before FDA approval. *See* Olmstead Rep. at 6 (citing Summary of Clinical Safety at 85, Tbl. 38). Dr. Olmstead admits that the table from the Summary of Clinical Safety is part of a much longer document, but he did not review the document in detail. *See* Olmstead Dep. at 42-43, 198. He also acknowledges that neither the table nor the data compilation reflected "any sort of analysis. They're just reporting counts, as far as I can tell." *Id.* at 197-98; *see id.* at 202-03 (noting the data compilation is "purely a listing" of all adverse events); Olmstead Rep. at 6 ("It does not appear Pfizer did any statistical testing of this data.").

Dr. Olmstead noted that the table on which he relied was incomplete and did not include data from all placebo-controlled trials completed prior to FDA approval. *See* Olmstead Rep. at 6 n.13 ("It is not clear why Pfizer did not include all available placebo data in the NDA submission."); Olmstead Dep. at 236 ("I never saw anything that explained it."). After being shown relevant portions of the Summary of Clinical Safety, he agreed that the document from which he pulled the table explained which trials Pfizer included in the table and why. *See* Olmstead Dep. at 238-40; Summary of Clinical Safety at 13-14. Dr. Olmstead did not review

the events from the trials that were not included in the table to see how, if at all, they would have affected his analysis. *See* Olmstead Dep. at 240-41.[1]

Dr. Olmstead claims that he selected the table and data compilations he used for his analyses because a Pfizer statistician had compiled those data. *See* Olmstead Rep. at 5; Olmstead Dep. at 213. He asserts that he "looked through" that statistician's deposition, but he could not recall what the statistician said about whether it was appropriate to use the data as a basis to analyze causation. *See* Olmstead Dep. at 182, 213-16, 290-91. The Pfizer statistician testified that "these tables are just used for screening values, not for any rigorous statistical analysis of any sort." Deposition of Dr. Simon Davies, Nov. 14, 2011, at 322 ("Davies Dep.") (Ex. 33). Further, Dr. Olmstead did not review FDA's reviews of the same data. *See* Olmstead Dep. at 199-200.

[1] For his 2007 and 2009 analyses, Dr. Olmstead relied on subsequent data compilations, which included the eight pre-approval clinical trials and added a number of trials Pfizer completed after FDA approval. *See* Olmstead Rep. at 6, 10, 12. In particular, Dr. Olmstead admitted that the 2007 and 2009 data compilations included all of the clinical trials from the 2005 data compilation, but the 2007 compilation added three placebo-controlled trials and one open-label trial, and the 2009 compilation added one more placebo-controlled trial. *See* Olmstead Dep. at 293, 320; Exhibit 15 to Deposition of Dr. Richard Olmstead, Mar. 21, 2012 (Ex. 46) (summarizing the depression-related data); Olmstead Dep. at 231-33, 293-95, 320-22 (verifying Exhibit 15).

B. Dr. Olmstead Lacks a Sufficient Basis to Conclude that There is a Valid Statistical Association Between the Use of Chantix and the Occurrence of Depression-Related Events.

In evaluating whether use of Chantix is associated with the occurrence of depression-related events, Dr. Olmstead makes a number of methodological errors, described below.

1. Dr. Olmstead Combines Uncontrolled Clinical Trial Data with Controlled Clinical Trial Data.

Before FDA approval, Pfizer conducted the A3051035 trial (Tonstad 2006), which included an uncontrolled, open-label phase in which all patients took Chantix followed by a controlled, double-blind phase in which half the patients took Chantix and half took a placebo. *See* Pfizer's Intro. & Statement of Facts Relevant to All *Daubert* Motions ("SOF") § III.A.2 (noting there were fewer depression-related events in patients continuing to take Chantix in the controlled, double-blind phase than in patients who switched to placebo). Dr. Olmstead admits that the design of the trial was unique, in that the patients taking placebo in the controlled, double-blind phase previously were exposed to Chantix for 12 weeks in the uncontrolled, open-label phase. *See* Olmstead Dep. at 246-48, 277-79. As a result, he testified that the trial is "not a particularly good trial to determine . . . a placebo control." *See id.* at 284.

In light of his opinion that Chantix causes depression-related events, Dr. Olmstead was asked whether he would expect there to be greater or fewer

depression-related events in patients taking Chantix compared to those taking placebo in the controlled, double-blind phase of the trial. He said he had "no idea" what to expect because "it's a different study design and a different set of patients." *Id.* at 277-78. "[T]he expectations in the 1035 study are difficult to figure out because of the design of the study to some degree." *Id.* at 282. When asked how he would interpret the results if the rates of depression-related events in the double-blind phase were lower in patients taking Chantix, he testified, "I don't know how I would interpret it." *Id.* at 281. Dr. Olmstead also admits it is not possible to calculate an odds ratio in a trial without a control group, such as the uncontrolled phase of the A3051035 trial, which he describes as providing "basically a raw estimate of depression-related events." *Id.* at 244, 279.

Notwithstanding the unique design of the A3051035 trial, Dr. Olmstead includes in his analyses the depression-related events that occurred during the uncontrolled, open-label portion of the trial, when patients only were taking Chantix, in three of his four analyses. *See id.* at 248-49, 302, 324, 336. The three analyses in which Dr. Olmstead lumps together the uncontrolled, open-label data with the placebo-controlled data from other trials are the only ones that showed a risk ratio greater than 2.0. *Compare* Olmstead Rep. at 8 *with* Olmstead Dep. at 9, 11, 13. Moreover, in counting events that occurred during the controlled, double-blind phase, Dr. Olmstead includes the events that occurred in the patients taking

Chantix, but *omitted* the events that occurred in patients taking placebo. *See* Olmstead Dep. at 242, 250-52, 288-89, 302-03, 337-38.

As a result of methods used by Dr. Olmstead in his analysis of data that existed before 2005, almost *half* of the events in Chantix patients – and a substantial portion of the events in his later analyses – came from the A3051035 trial. *See id.* at 243. Similarly, if he had included the events that occurred in the placebo patients during the controlled, double-blind phase of the A3051035 trial, the number of events in placebo patients would have more than doubled. *See id.* at 288-89. Dr. Olmstead could not say how adding those placebo events would have affected his results. *See id.* at 338.

For his 2007 and 2009 analyses, Dr. Olmstead includes another open-label trial – the trial comparing Chantix to the nicotine patch – using a similar method. *See* SOF § III.A.2 (describing the A3051044 trial (Aubin 2008)). As with the A3051035 trial, Dr. Olmstead cannot predict whether the rates of depression-related events would be higher in patients taking Chantix than in those using the nicotine patch. *See* Olmstead Dep. at 304 ("I don't know if I would have an expectation."). Because there were no placebo patients in the A3051044 trial, he admits he could not calculate an odds ratio comparing Chantix to placebo. *See id.* at 298. Yet Dr. Olmstead counts only the depression-related events that occurred in patients taking Chantix; he does not include any events in the patients taking

NRT. *See id.* at 297-98, 318. His method thus results in counting a number of events against Chantix and none against placebo, even though patients taking Chantix in the trial were *less* likely to suffer depression-related events than those using the nicotine patch. *See id.* at 314-15.

In contrast, no other peer-reviewed meta-analysis of the Chantix data has combined the open-label trial data with placebo-controlled trials. For example, the Cochrane Collaboration, an organization which Dr. Olmstead admits has promulgated generally accepted standards for performing meta-analyses, excluded both trials in both its 2011 and 2012 meta-analyses of the Chantix data. *See* Cahill et al., COCHRANE DATABASE SYS. REVS. 2012, Issue 4 at 8, 86-90 ("Cahill 2012") (Ex. 69); Cahill et al., COCHRANE DATABASE SYS. REVS. 2011, Issue 2 at 7 ("Cahill 2011") (Ex. 68); Olmstead Dep. at 265-68. In their recent evaluation of all serious adverse events, the Cochrane authors included data from both arms of the controlled, double-blind phase of the A3051035 trial, but they did not include any of the data from the uncontrolled, open-label phase of the trial. *See* Cahill 2012 at 94 (listing only approximately 600 subjects in each arm during the controlled, double-blind phase).

Similarly, in recent meta-analyses of the Chantix cardiovascular data, both Dr. Furberg and Dr. Prochaska included data only from the controlled, double-blind phase of the A3051035, and neither set of researchers included the open-label

NRT trial. *See* Singh & Furberg et al., CMAJ 2011;183:1359-66, at 1360 ("Singh") (Ex. 113); Prochaska et al., BRIT. MED. J. 2012;344:e2856, at 11 ("Prochaska") (Ex. 104). Finally, Dr. Tonstad, an independent researcher, and Pfizer scientists – including the statistician whose tables formed the basis for Dr. Olmstead's analyses – did not include either trial in the 10-trial meta-analysis published in 2010. *See* Tonstad et al., DRUG SAFETY 2010;33:289-301, at 292 ("Tonstad 2010") (Ex. 118); Olmstead Dep. at 245-46, 328-29.

2. Dr. Olmstead Uses Unreliable Methods to Determine Whether His Results Are Due to the Play of Chance.

Dr. Olmstead also uses methods that relax the accepted threshold for statistical significance, which inflates the error rate associated with his analysis and affects the reliability of his results. First, he uses a statistical test known as "Fisher's exact test" to calculate all of the p-values in his report, even though that test treats the data as if it all came from a single trial, rather than a test that properly recognizes that the data came from different trials. *See* Olmstead Dep. at 158, 160-61, 164-66. In the peer-reviewed medical community, Dr. Olmstead never has used the Fisher's exact test to combine data across clinical trials, nor can he identify any meta-analysis that uses that test to combine data across trials. *See id.* at 166-68, 173, 176-77.

Rather, Dr. Olmstead admits, and Plaintiffs' other experts acknowledge, that a different statistical test, known as "Mantel-Haenszel," is the appropriate test to

use in a meta-analysis. *See id.* at 168-69, 261; Deposition of Dr. Shira Kramer, Mar. 9, 2012, at 122-23 ("Kramer Dep.") (Ex. 41). Consistent with those acknowledgements, all peer-reviewed meta-analyses related to Chantix use the Mantel-Haenszel test, including the meta-analyses by the Cochrane Collaboration, Dr. Furberg, Dr. Prochaska, and Dr. Tonstad. *See* Cahill 2012 at 5; Cahill 2011 at 4; Singh at 1361; Prochaska at 2-3; Tonstad 2010 at 293. Dr. Olmstead does not know how use of a Mantel-Haenszel test would have changed his results. *See* Olmstead Dep. at 160-61.

Second, Dr. Olmstead calculates approximately 150 tests for statistical significance, but he does not make any adjustments to correct for the inflated error rate that results from that many statistical tests. *See* Olmstead Rep. at 8, 9, 11, 13, 15; Olmstead Dep. at 114, 119, 203-04; SOF § II.B.2 (describing the problem of multiple comparisons). Another Plaintiffs' expert even recommended that Dr. Olmstead adjust his statistical significance threshold by using a method (Bonferroni correction) to control his error rate, but Plaintiffs' counsel and Dr. Olmstead rejected that suggestion. *See* Deposition of Dr. William C. Wirshing, Mar. 23, 2012, at 295-99 ("Wirshing Dep.") (Ex. 47).

3. Dr. Olmstead Fails to Account for the Confounding Effect of Nicotine Withdrawal.

Dr. Olmstead also fails to address the possibility that his results are due to the confounding effects of nicotine withdrawal. He concedes that more smokers

quit while taking Chantix in the clinical trials and that quitting is associated with nicotine withdrawal effects, *see* Olmstead Dep. at 85-86; SOF § III.A.2, but he does not adjust for that confounding factor. His statistical analyses are "all based on the raw data as supplied in those tables and does not take into account smoking status." *Id.* at 338-39. As a result, he cannot tell how, if at all, his results would have changed if he had only included patients who quit smoking or only those who continued smoking. *See id.*

C. Dr. Olmstead Lacks a Sufficient Basis to Conclude that Chantix Causes Depression-Related Events.

Even if a valid statistical association existed, Dr. Olmstead fails to consider important factors in assessing whether that association reflects a causal relationship. He does not consider the totality of the available data to see whether his results are consistent with the available clinical trials or observational studies, and he ignores the principle of a dose-response relationship.

1. Dr. Olmstead Fails to Consider the Totality of Clinical Trial Data and Fails to Consider Observational Study Data At All.

Dr. Olmstead does not perform a comprehensive review of all the available clinical trial data, even though he knew additional trials were available at the time he completed his report. *See* Olmstead Dep. at 55. Even his most recent analysis includes only 10 of the 16 placebo-controlled clinical trials available today, which means he excludes more than 2,400 patients from his analysis. *See id.* at 183;

Expert Rebuttal Report of Dr. Richard E. Olmstead, Feb. 3, 2012, at App. A (listing number of patients in each study) ("Olmstead Reb. Rep.") (Ex. 14). He did not consider the data for all 16 trials until he reviewed Pfizer's experts' reports, and he does not perform any statistical analysis on the six trials completed after 2008. *See* Olmstead Dep. at 17, 49-50. He also concedes that he cannot tell how his results would have differed if he were to include all available placebo-controlled data. *See id.* at 334-35.

In his rebuttal report, Dr. Olmstead attempts to rationalize his failure to include all the available data. In particular, he claims that: (1) the six trials that he ignores were conducted after there was publicity about neuropsychiatric adverse event reports, which he speculates discouraged patients at psychiatric risk from participating in the Chantix trials; and (2) those trials (and others) are not generalizable because they involve different populations of patients (namely, patients outside the United States or those with psychiatric or other illnesses) or different study designs. *See* Olmstead Reb. Rep. at 2-8.

Dr. Olmstead admits he cannot cite any data to support his claim that publicity about Chantix affected the recruitment of patients. *See* Olmstead Dep. at 377. In fact, his own report acknowledges that the rates of depression-related events are *higher* in the more recent trials that he ignores. *See id.* at 296; Olmstead Reb. Rep. at 6 (A3051072), 7 (A3051095), & 8 (A3051115).

Although Dr. Olmstead ignores the later trials on the additional ground that they were conducted outside of the United States, his own analysis includes patients treated in foreign countries. *See* Olmstead Reb. Rep. at 5 & n.2. Further, he concedes that at least some of the more recent trials improved the generalizability of the Chantix data, meaning that those trials provide more information about the effects of Chantix in a broader range of smokers. *See* Olmstead Dep. at 373-75.

Dr. Olmstead's failure to include all available placebo-controlled clinical trials also stands in stark contrast to the peer-reviewed medical literature. For example, the Cochrane Collaboration included in its analyses data from placebo-controlled trials conducted after 2008 and in foreign countries. *See* Cahill 2011 at 5, 7; Cahill 2012 at 6, 8; Olmstead Dep. at 124-25, 258; *see also* SOF § II.A.2 (noting that meta-analyses should include all available controlled trials).

Dr. Olmstead's approach also departs from the methodology of Plaintiffs' expert Dr. Furberg, who includes all available placebo-controlled trials in his Chantix meta-analysis of cardiovascular events. *See* Furberg Dep. at 18-19; Singh at 1361. And just two weeks ago, independent researchers published another meta-analysis related to the cardiovascular safety of Chantix, which also includes the trials Dr. Olmstead omits from his analysis. *See* Prochaska at 11. Dr. Olmstead's approach also is contrary to the peer-reviewed methods used by Dr. Tonstad and

several Pfizer scientists – including the statistician who assembled some of the tables that are the basis of Dr. Olmstead's opinions. *See* Tonstad 2010 at 292.

Finally, Dr. Olmstead testified that none of the clinical trial data "is definitive for . . . the overall question." Olmstead Dep. at 365. When asked how he would evaluate the neuropsychiatric safety of Chantix, he stated, "I'd do a new trial and do a large observational trial. That would be . . . the definitive thing." *Id.* Yet Dr. Olmstead failed to review *any* of the available observational study data, including FDA-sponsored and other observational studies that show no evidence of an association. *See id.* at 17, 39-40.

2. Dr. Olmstead Combines All Doses of Chantix and Ignores the Principle of a Dose-Response Relationship.

For his first analysis of data from 2005 (from Table 38 in the Summary of Clinical Safety), Dr. Olmstead combines all doses of Chantix – even though Table 38 lists the lower doses separately from the higher dose and shows that patients taking lower doses experienced *higher* rates of depression-related events than those taking higher-doses. *See* Olmstead Rep. at 8; Olmstead Dep. at 219, 222-23; Summary of Clinical Safety at 85. In all his other analyses, he also combines all doses of Chantix. *See* Olmstead Dep. at 335-36. Dr. Olmstead does not perform any analysis to separate the data by dose, and he does not know how his results might have changed had he done so. *See id.* at 222, 336.

When asked whether the incidence of a causally-related adverse event generally should increase with higher doses, Dr. Olmstead would "not necessarily" agree. *Id*. at 216. However, when asked to identify any example of a medication where a causal relationship is established and patients taking higher doses of the medication experience fewer of the adverse event in question, he could not identify one. *See id.* at 217-18. Ultimately, Dr. Olmstead concedes that he does not have any evidence to support a theory that Chantix causes more suicide and depression at lower doses. *See id.* at 226.

ARGUMENT

Plaintiffs cannot prove general causation without expert testimony, and they bear the burden of proving by a preponderance of the evidence that their experts' opinions are admissible under *Daubert* and Rule 702. *See Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593 n.10 (1993); Fed. R. Evid. 702. Under Rule 702, testimony is only admissible if "(1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the expert has reliably applied the principles and methods to the facts of the case." Fed. R. Evid. 702. To satisfy this standard, Plaintiffs must show that their experts' opinions are both reliable and relevant. *See Daubert*, 509 U.S. at 590, 593-97.

For expert testimony to be reliable under *Daubert*, the "methodology underlying the testimony [must be] scientifically valid." *Id.* at 592-93; *see*

Kilpatrick v. Breg, Inc., 613 F.3d 1329, 1336 (11th Cir. 2010). "The proposed testimony must derive from the scientific method; good grounds and appropriate validation must support it." *McClain*, 401 F.3d at 1237. This requirement of reliability is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002).

In *Daubert*, the Supreme Court identified four factors that courts may use to make this determination: (1) whether the theory can and has been tested; (2) whether it has been subject to peer-review; (3) the known or expected rate of error; and (4) whether the theory or methodology is generally accepted in the relevant scientific community. *See Daubert*, 509 U.S. at 593-94; *Rider*, 295 F.3d at 1197. The reliability requirement is designed "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). In other words, there cannot be a double standard between courtroom science and real-world science, and a litigation expert cannot employ a methodology that is not followed by real-world scientists in the same field.

To be relevant, expert opinions "must assist the trier of fact to understand or determine a fact in issue." *Daubert*, 509 U.S. at 592. In other words, even if a methodology is reliable, the expert still must apply that methodology faithfully to

the facts of the case, which some courts have called the "fit" requirement. *See id.* at 591; Fed. R. Evid. 702. That a methodology is acceptable for some purposes does not mean it is acceptable for others. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997); *Rider*, 295 F.3d at 1197. A district court "may not admit evidence when there is 'simply too great an analytical gap between the data and the opinion proffered.'" *Rider*, 295 F.3d at 1197 (quoting *Joiner*, 522 U.S. at 146).

In analyzing reliability and relevance, "*Daubert* requires the trial court to act as a gatekeeper to insure that speculative and unreliable opinions do not reach the jury." *McClain*, 401 F.3d at 1237; *see Daubert*, 509 U.S. at 589 n.3. District courts must act as the gatekeepers of expert testimony because such evidence "can be both powerful and quite misleading" to juries. *Daubert*, 509 U.S. at 579, 595.

In performing their gatekeeping role, district courts must not "simply rubber stamp the opinions of expert witnesses once they are determined to be an expert." *Kilpatrick*, 613 F.3d at 1336; *see also Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316-17 (11th Cir. 1999). While courts may be reluctant to "don[] white coats and mak[e] determinations that are outside their field of expertise, the Supreme Court has obviously deemed this less objectionable than dumping a barrage of questionable scientific evidence on a jury, who would likely be even less equipped than the judge to make reliability and relevance determinations and more likely than the judge to be awestruck by the expert's mystique." *Allison*, 184

F.3d at 1310; *see Daubert*, 509 U.S. at 597 ("We recognize that . . . a gatekeeping role for the judge . . . inevitably on occasion will prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes.").

It is particularly important for courts to play this gatekeeping role where, as here, a product remains on the market and the data continue to evolve. "Given time, information, and resources, courts may only admit the state of science as it is. Courts are cautioned not to admit speculation, conjecture, or inference that cannot be supported by sound scientific principles." *Rider*, 295 F.3d at 1202. "'The courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it.'" *Rider*, 295 F.3d at 1202 (quoting *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996)).

Here, the Court should exclude Dr. Olmstead's causation opinions because he departed from undisputed, accepted principles in analyzing this type of scientific evidence, and he reached his conclusions based on improper methods. As a result, his opinions are unreliable and the Court should exclude them.

I. THE COURT SHOULD EXCLUDE DR. OLMSTEAD'S CAUSATION OPINIONS BECAUSE HE HAS NO RELIABLE BASIS TO CONCLUDE THERE IS A VALID STATISTICAL ASSOCIATION BETWEEN THE USE OF CHANTIX AND DEPRESSION

Before a researcher can conclude that a medication causes an adverse event, he first must establish that there is a valid statistical association between exposure to the medication and the event of interest. *See* SOF § II.B. Here, for three reasons, Dr. Olmstead lacks a reliable basis to conclude that there is a valid statistical association between Chantix and depression. First, Dr. Olmstead manufactures a statistical association by improperly combining uncontrolled and controlled clinical trial data. Second, he uses unreliable statistical methods, which do not fit the data and inflate the error rate of his analysis. Third, Dr. Olmstead does not account for a key confounding factor – the higher rates of quitting and, as a result, nicotine withdrawal effects.

A. Dr. Olmstead Improperly Combines Uncontrolled Clinical Trial Data with Controlled Data.

The Court should exclude Dr. Olmstead's causation opinions because he improperly combines uncontrolled clinical trial data with controlled data. Dr. Olmstead lumps in depression-related events from the uncontrolled, open-label phase of the A3051035 trial, even though there was no control group against which to compare the incidence of those events – which is the equivalent of holding a general election in which only members of one political party are allowed to vote

in a large number of precincts. He also counts the events in Chantix patients during the controlled, double-blind phase of that trial, but he omits any events that occurred in placebo patients – which is like counting only the votes cast by members of one political party in other precincts. By choosing these invalid methods, which depart from the methods used by researchers in every other Chantix meta-analysis published in the peer-reviewed literature, Dr. Olmstead intentionally doubles the number of depression-related events in Chantix patients in his 2005 analysis, while cutting the number of placebo events in half.

1. The Court Should Exclude Dr. Olmstead's Causation Opinions In Their Entirety Because He Relies on Uncontrolled Data, Which Cannot Account for the Background Risk of Neuropsychiatric Events.

Because "suicide [and depression] occur in the general population," *Rimbert v. Eli Lilly & Co.*, No. CIV 06-0874, 2009 WL 2208570, at *11, (D. N.M. July 21, 2009), "[a] reliable methodology should take into account the background risk." *McClain*, 401 F.3d at 1243. "The background risk is not the risk posed by the chemical or drug at issue in the case. It is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges *without* exposure to the drug or chemical in question." *Id*. (emphasis in original). Without information about the background risk, "the trier of fact cannot determine, from [the expert's] opinion, whether the claimed injury was from the medicine or

from some other background risk factor." *In re Trasylol Prods. Liab. Litig.*, No. 08-MD-01928, 2010 WL 4052141, at *2 (S.D. Fla. May 12, 2010).

To account for the impact of background risk, researchers use controlled clinical trials and observational studies to compare those taking a medication to those who are not. *See* SOF §§ II.A.1, II.A.2, & II.B.1. Studies that "lack controls . . . do not provide as much information as controlled epidemiological studies." *McClain*, 401 F.3d at 1253; *see Kilpatrick*, 613 F.3d at 1338. As the REFERENCE MANUAL recognizes, "data from a treatment group without a control group generally reveal very little and can be misleading." REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 220 (3d ed. 2011) ("REF. MAN.").

Here, because suicide and depression occur every day in smokers trying to quit without medication, smokers trying to quit with Chantix must be compared to a control group of smokers trying to quit without Chantix. *See Rimbert*, 2009 WL 2208570, at *11; *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1224 (D. Colo. 1998) ("Without a controlled study, there in no way to determine if these symptoms are more common in women with silicone breast implants than women without implants."). For these reasons, courts in the Eleventh Circuit routinely exclude expert opinions that rely on uncontrolled data and fail to take background risk into account. *See McClain*, 401 F.3d at 1244; *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1355 (S.D. Fla. 2011); *In re Trasylol*, 2010 WL

4052141, at *2; *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1301 (M.D. Fla. 2007).

In light of the importance of using controlled data, every Chantix meta-analysis published in the peer-reviewed literature – including those authored by the Cochrane Collaboration, Plaintiffs' expert Dr. Furberg, Dr. Prochaska, and Dr. Tonstad – either exclude the A3051035 trial altogether or include only data from the controlled, double-blind phase. None of them follow Dr. Olmstead's method of including data from the uncontrolled, open-label phase or counting events only from Chantix patients in the controlled, double-blind phase. As Dr. Furberg explains, including uncontrolled data in an analysis of clinical trials is "nonscientific" and "a dumb idea." Deposition of Dr. Curt Furberg, Mar. 28, 2012, at 36-37 ("Furberg Dep.") (Ex. 39); *see* SOF § II.A.2 (noting meta-analyses should only include controlled data).

On the basis of controlled clinical trial data, European regulators concluded that "the current evidence does not support a causal link," and the Cochrane Collaboration found there is "little evidence" of a link between Chantix and neuropsychiatric events. CHMP Final Assessment Report, Jan. 22, 2009, at 10 ("CHMP Final Assessment") (Ex. 55); Cahill 2012 at 14. Similarly, using controlled data only, two FDA observational studies found that Chantix is no less safe than the nicotine patch, and the FDA asked Pfizer to conduct another trial

because a causal relationship had not been established. These conclusions, which are based on controlled data and are contrary to Dr. Olmstead's opinions, demonstrate just how Dr. Olmstead manipulated his methods to fit a desired result. Indeed, if Dr. Olmstead's analysis of the data were reliable, the current clinical trials requested by FDA and EMA and approved by hundreds of investigators and IRBs around the world could not ethically be conducted. *See* Deposition of Dr. Russell V. Luepker, Feb. 29, 2012, at 215-17 ("Luepker Dep.") (Ex. 43); Furberg Dep. at 225-26; FRIEDMAN & FURBERG ET AL., FUNDAMENTALS OF CLINICAL TRIALS 20-21 (4th ed. 2010) ("FRIEDMAN") (Ex. 77).

By combining controlled and uncontrolled data and failing to account for background risk, Dr. Olmstead does not employ in the courtroom "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152; *see Rider*, 295 F.3d at 1197 (excluding an expert who did not use "sound scientific principles"). Accordingly, Dr. Olmstead's methods "may properly be viewed with skepticism," *Daubert*, 509 U.S. at 594, and the Court should exclude his causation opinions in their entirety.

2. The Court Should Exclude Any Opinion that Chantix "Doubles the Risk" of Depression-Related Events.

Even if the Court does not exclude Dr. Olmstead's causation opinions in their entirety, the Court should nonetheless preclude Dr. Olmstead and other Plaintiffs' experts from testifying that Chantix "doubles the risk" of depression-

related events. Dr. Olmstead's analyses only show a relative risk above 2.0 when he combines uncontrolled data with controlled data.

An "important test" under *Daubert* is the "analytical 'fit' between the methodology used and the conclusions drawn." *Rider*, 295 F.3d at 1197 (citing *Joiner*, 522 U.S. at 146). "Trained experts commonly extrapolate from existing data," but their opinions cannot be "connected to existing data only by the *ipse dixit* of the expert." *Joiner*, 522 U.S. at 146. Where "there is simply too great an analytical gap between the data and the opinion offered," an expert's opinion is unreliable. *Id.*; *see Rider*, 295 F.3d at 1197; *McClain*, 401 F.3d at 1255.

To demonstrate reliability, Dr. Olmstead must explain the "fit" between his analysis of Pfizer tables from 2005, and his conclusion that Chantix "doubles the risk" of depression-related events. *See Joiner*, 522 U.S. at 146; *Rider*, 295 F.3d at 1197. But Dr. Olmstead does not explain why it is methodologically appropriate to include uncontrolled data with controlled data, other than observing that he simply uses the tables that a Pfizer statistician assembled more than seven years ago. Dr. Olmstead ignores that the tables never were intended for "any rigorous statistical analysis of any sort." Davies Dep. at 322. Dr. Olmstead also does not explain why it was proper to rely on these outdated tables when other, more rigorous data from 16 randomized, controlled clinical trials are currently available. *See* Olmstead

Dep. at 17, 49-50. Dr. Olmstead simply offers his own *ipse dixit* that he relies on outdated and incomplete tables because Pfizer employees compiled them.

Because Dr. Olmstead provides no analytical "fit" between his analysis of the tables, which include uncontrolled data, and his conclusion that Chantix "doubles the risk" of depression-related events, his opinions are unreliable. *See Joiner*, 522 U.S. at 146; *Rider*, 295 F.3d at 1197; *Kilpatrick*, 613 F.3d at 1338. Accordingly, the Court should preclude Dr. Olmstead and other experts from giving opinions that are based on such evidence.

B. Dr. Olmstead Uses Unreliable Methods to Determine Whether There Is a Valid Statistical Association Between the Use of Chantix and the Occurrence of Depression-Related Events.

The Court also should exclude Dr. Olmstead's causation opinions because he does not use reliable, generally accepted methods to determine whether his results could be due to chance, as opposed to a true causal effect. The reliability of an expert's methodology depends, in part, on the general acceptance of that methodology by the relevant scientific community. *See Daubert*, 509 U.S. at 594. Courts should consider whether an expert bases his opinions on a "known technique," whether that technique has "general acceptance" by experts in the field, and the error rate of the technique. *Id*. It is unreliable for an expert to base his opinions on a method that departs from the "intellectual rigor that characterizes

the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152; *see McClain*, 401 F.3d at 1248.

Here, in order to produce a statistically significant result, Dr. Olmstead uses a statistical test for assessing the likelihood that his results are due to the play of chance (a Fisher's exact test), which treats the data as if they all come from one trial – even though they do not. *See* Olmstead Dep. at 158, 160-61, 164-66. His method departs from the generally accepted statistical test endorsed by Plaintiffs' other experts and consistently used by scientists in the field when combining data from multiple trials (the Mantel-Haenszel test), as evidenced by every Chantix meta-analysis published in the peer-reviewed medical literature. Because the data Dr. Olmstead analyzes does not come from one trial, he also does not apply his methods "reliably to the facts of the case." Fed. R. Evid. 702.

Dr. Olmstead also does not adjust his methods, or at least qualify his opinions, to account for the large number of statistical tests he performed, even though other Plaintiffs' experts recommend doing so. This faulty method inflates the error rate of his analyses and relaxes the standard necessary to declare his results statistically significant. *See Daubert*, 509 U.S. at 594 ("In the case of a particular scientific technique, the court ordinarily should consider the known or potential rate of error.").

Courts in the Eleventh Circuit have excluded experts who base their opinions on methodologies that neither account for the error rate nor attain general acceptance within the scientific community. *See, e.g.*, *Sumner v. Biomet, Inc.*, 434 F. App'x 834, 842 (11th Cir. July 15, 2011); *Jaquillard v. Home Depot, U.S.A*, No. CV 410-167, 2012 WL 527421, at *7 (S.D. Ga. Feb. 16, 2012); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1355-56 (N.D. Ga. 2001). Because Dr. Olmstead uses statistical methods and standards that depart from those used in his field, his causation opinion should be excluded as a matter of law.

C. Dr. Olmstead Fails to Account for the Confounding Effects of Nicotine Withdrawal.

Even if Dr. Olmstead had established a statistically significant "doubling of the risk" based on reliable methods, he would still have to provide a reliable basis for concluding that the risk was due to Chantix and not the effects of nicotine withdrawal. As the FDA acknowledges, it is "difficult to evaluate" the Chantix adverse event data because "people who stop smoking without using medications may also experience similar type symptoms due to nicotine withdrawal." Dr. Curtis Rosebraugh, FDA Tr., July 1, 2009, at 2 (Ex. 133). Dr. Olmstead admits that more smokers quit while taking Chantix and that quitting leads to nicotine withdrawal effects, but he does not even attempt to account for that confounding effect in his analysis of the depression-related events.

A statistical association "is not enough to warrant a causal inference;" possible reasons for an association include "causation, confounding, and coincidence." REF. MAN. at 264. Therefore, a scientist "must account for the roles of bias, confounding factors, and the likelihood that the observed association is due to chance" in demonstrating the reliability of his opinions. *Magistrini*, 180 F. Supp. 2d at 604.

In *Joiner*, the Supreme Court held that a district court properly excluded an expert's opinion that was based on an epidemiological study in which the subjects had been exposed to a number of carcinogenic substances in addition to the one at issue, even though the results of the study were statistically significant. 522 U.S. at 146. Similarly, Dr. Olmstead should be excluded from testifying on the bases of his analyses – even if they were statistically significant – because he fails to consider the confounding effect of nicotine withdrawal.

II. THE COURT SHOULD EXCLUDE DR. OLMSTEAD'S CAUSATION OPINIONS BECAUSE HE LACKS A RELIABLE BASIS TO CONCLUDE THAT ANY DIFFERENCE HE OBSERVED REFLECTS A CAUSAL RELATIONSHIP

Even if Dr. Olmstead had established a valid statistical association, he fails to consider essential factors in assessing whether any such association was causal, including whether the association is replicated in and consistent across the totality of available data and whether the association demonstrates a dose-response relationship. *See* SOF § II.C. Rather than consider these factors, Dr. Olmstead

cherry-picks a fraction of the available evidence to justify his causation opinion. As a result, Dr. Olmstead's statistical analyses of clinical trial data are unreliable, and the Court should exclude his opinion that Chantix causes depression-related events and preclude the testimony of others who relied on his analyses.

A. Dr. Olmstead Ignores the Principles of Replication and Consistency and Instead Cherry-Picks Selective Portions of the Available Clinical Trial Data, While Ignoring Observational Study Data All Together.

In a post-hoc effort to fit a desired result, Dr. Olmstead fails to consider the totality of clinical trial data today. His earliest analysis includes only four placebo-controlled trials, and even his analysis of data from early 2009 includes only 10 of the 16 available placebo-controlled trials – thereby excluding approximately one-third of the available data. Dr. Olmstead admits that he did not perform any statistical analysis of the six trials completed after 2008, and he only reviewed the totality of the clinical trial data when he read Pfizer's experts' reports. He ignores the independent conclusions of European regulators and the Cochrane Collaboration that the clinical trial data do not support a causal link between Chantix and neuropsychiatric events. He also ignores the results of FDA-sponsored observational studies that provide no evidence of an association. Dr. Olmstead's approach – looking only at data available at earlier points in time – is the equivalent of declaring a winner of an election based purely on votes cast before noon on election day.

In *McClain*, the Eleventh Circuit reversed a district court for failing to exclude an expert who drew "unauthorized conclusions from limited data." 401 F.3d at 1248. As the Court explained, scientists do not "leap to specific conclusions about causation or toxicity from incomplete evidence or broad principles . . . ." *Id*. Rather, they should consider the totality of the available evidence. *See In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004).

Indeed, courts exclude expert testimony "where the expert selectively chose his support from the scientific landscape." *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) (quoting *Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999)). It is unreliable for an expert to cherry-pick and select "study data that best support[s] her opinion, while downplaying contrary findings or conclusions." *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 892 (E.D. Ark. 2010).[2] Similarly, "no reliable scientific approach can simply ignore the epidemiology that exists." *Perry v. Novartis*

[2] *See also Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 886 (10th Cir. 2005) (excluding experts' testimony because "both experts ignored or discounted without explanation the contrary epidemiological studies"); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (excluding expert for "cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion"); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1032-34 (S.D. Ill. 2001) (rejecting experts' opinions "inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies").

Pharms. Corp., 564 F. Supp. 2d 452, 465-66 (E.D. Pa. 2008); *see Rimbert*, 2009 WL 2208570, at *13-14 (excluding expert who "was aware of a body of published medical and scientific literature, including controlled clinical trials [that] she did not consider" in forming her opinions). An expert who engages in such "selective use of facts fails to satisfy the scientific method and *Daubert*." *Barber v. United Airlines, Inc*., 17 F. App'x 433, 437 (7th Cir. 2001).

Dr. Olmstead's methods also depart from the methods used in the peer-reviewed medical community, as demonstrated by the independent meta-analyses performed by the Cochrane Collaboration, Dr. Prochaska, and even the meta-analysis published by Plaintiffs' expert Dr. Furberg. All of these meta-analyses include the available placebo-controlled clinical trials, including those conducted after 2008 and in foreign countries. By excluding later clinical trials and ignoring the observational studies all together, Dr. Olmstead cherry-picks the data that allow him to "draw [ ] unauthorized conclusions from limited data . . . ." *McClain*, 401 F.3d at 1248.

Where, as here, an expert's litigation methodology does not reflect "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," district courts must exclude the expert under *Daubert*. *Kumho Tire*, 526 U.S. at 152. The clear contrast between Dr. Olmstead's litigation methods and those used by every researcher who analyzed the Chantix data outside the

courtroom demonstrates that Dr. Olmstead's methods are not generally accepted and "may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Dr. Olmstead also attempts to justify the trials he selected only after being challenged by Pfizer's experts, which this court should find "troubling." *Haller v. AstraZeneca Pharms. LP*, 598 F. Supp. 2d 1271, 1296-97 (M.D. Fla. 2009) (finding it "troubling . . . that the underpinnings of [the expert's] opinions have changed in direct response to [defendant's] motion practice").

When an expert fails to consider the totality of the evidence in forming his opinion, there is "simply too great an analytical gap between the data and the opinion proffered." *Joiner*, 522 U.S. at 146; *McClain*, 401 F.3d at 1248. At the very least, because Dr. Olmstead does not review all the available data, the Court should preclude him (or others relying on his analyses) from opining that Chantix "doubles the risk" of depression-related events or that the increased risk he claims he observes did not change appreciably over time.

B. Dr. Olmstead Ignores the Principle of Dose Response.

The Court also should exclude Dr. Olmstead's causation opinions because he ignored the principle of a dose-response relationship – undoubtedly because there is no evidence of one. The dose-response relationship is "the hallmark of the science of toxic torts." *McClain*, 401 F.3d at 1240. According to the Eleventh Circuit, it is "the single most important factor to consider in evaluating whether an

alleged exposure caused a specific adverse effect." *Id.* at 1242 (quoting David L. Eaton, *Scientific Judgment and Toxic Torts – A Primer in Toxicology for Judges and Lawyers*, 12 J. L. & POL'Y 5, 15 (2003)); *see In re Accutane*, 511 F. Supp. 2d at 1293 ("Dose is critical to any evaluation of toxicity of a drug").

In *McClain*, the Eleventh Circuit reversed the district court for failing to exclude the testimony of an expert who did "not follow the basic methodology that scientists use to determine causation – the dose response relationship." *McClain*, 401 F.3d at 1242. A court should "pay careful attention to the expert's testimony about the dose-response relationship" when analyzing an expert's methodology, and an expert who "avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology." *Id.* at 1241-42. Since *McClain*, the Eleventh Circuit and district courts repeatedly have excluded experts who failed to consider the dose-response relationship. *See, e.g.*, *Kilpatrick*, 613 F.3d at 1339 ("The lack of any data or any explanation by [plaintiff's expert] on this [dose-response] point puts the methodology of . . . [plaintiff's expert's] general causation opinions in question."); *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d at 1353 ("[T]here is no dose-response evidence . . . to reliably infer what type of exposure level to Fixodent is necessary . . . to cause a myelopathy."); *In re Accutane*, 511 F. Supp. 2d at 1293.

Here, the primary table on which Dr. Olmstead relies shows a complete absence of a dose-response relationship. In fact, patients taking lower doses of Chantix experienced a *higher* rate of depression-related events – a finding that is at odds with a true causal relationship. Dr. Olmstead does "not follow the basic methodology" that requires an analysis of dose. *McClain*, 401 F.3d at 1241-42; *Kilpatrick*, 613 F.3d at 1339.

CONCLUSION

Dr. Olmstead's causation opinions are inadmissible because they are based on unreliable methods and are not based on the totality of scientific evidence today. As a result, the Court should exclude Dr. Olmstead's testimony in its entirety. In the alternative, the Court should preclude Dr. Olmstead from testifying that Chantix doubles the risk of depression-related events or that evidence of an increased risk was available as of 2005.

Dated: May 18, 2012

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on May 18, 2012, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF system which will send notification to the attorneys of record.

s/ Andrew B. Johnson
OF COUNSEL